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Health and Environmental Effects Profile for Chloranil

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16. ABSTRACT

The Health and Environmental Effects Profile for Chloranil was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Chloranil has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for chloranil is 4.03×10^{-1} $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for chloranil is 1000.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CHLORANIL

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

Chloranil is a yellow crystalline solid with a weak characteristic odor (Latypova, 1976). It has a water solubility of 250 mg/ℓ at room temperature but is readily soluble in ether (Martin and Worthing, 1977). Chloranil is chemically stable under normal conditions; however, two of the four chlorine atoms in the para-position are easily substituted under certain reaction conditions (Windholz, 1983).

Although the TSCA Inventory (U.S. EPA, 1977a) lists five companies as importers of chloranil in the United States prior to 1977, currently this chemical is not produced in the United States (SRI, 1985; USITC, 1984). Aceto Chemical Co., Inc., Flushing, NY, the only U.S. producer of pesticide products containing chloranil, cancelled its U.S. EPA registration in February, 1977 (U.S. EPA, 1977b). Chloranil is manufactured by treating phenol, p-chlorophenol or p-phenylenediamine with potassium chlorate and hydrochloric acid (Hawley, 1981). The present uses for this chemical in the United States appear to be limited to dye and electrode manufacture, and as a chemical reagent (Hawley, 1981).

The fate and transport of chloranil in the environment has not been studied comprehensively. Based on its physical properties and the limited aquatic reactivity data available, chloranil is not expected to undergo significant chemical or photochemical reactions in the atmosphere. It has also been speculated that small amounts of chloranil will be removed from the atmosphere through wet deposition and that other physical removal mechanisms are not likely to be important. Therefore, chloranil is expected to persist in the atmosphere.

From the limited data provided by Fisch and Hemmerlin (1972), it has been concluded that chloranil will undergo significant photochemical reaction in aquatic media. Biodegradation of chloranil in aquatic media may also be an important process (Oduntan and Odeyemi, 1984). The half-lives for chloranil disappearance from sterile and nonsterile sewage water have been estimated to be 7 and 4 days, respectively. The corresponding values in freshwater are 8 and 5 days, but the half-life of chloranil in seawater has been estimated to be 18 weeks. Therefore, chloranil may not persist in most natural freshwaters, but it may be persistent in seawater (Oduntan and Odeyemi, 1984). Based on its physical properties, it is expected that in aquatic media a significant loss of chloranil will not occur through volatilization, but moderate removal of chloranil will occur through precipitation of sorbed chloranil into aquatic particulate matters. Chloranil will not bioconcentrate significantly in aquatic organisms.

In the soil, significant removal of chloranil will take place through biodegradation. The overall half-life of chloranil in soil has been estimated to be 6 days (Oduntan and Odeyemi, 1984). The experimental results of Helling et al. (1974) show that chloranil will have a low mobility in soil. Based on its mobility and significantly high biodegradation rate in soil, chloranil probably will not leach into groundwater under most conditions.

Pertinent data regarding the level of chloranil in any environmental medium could not be located in the available literature as cited in the Appendix. Since chloranil is no longer manufactured in the United States, the principal sources of chloranil in the environment are expected to be user sites, such as dye and electrode manufacturers. Small amounts of chloranil may also originate from the photodecomposition of pentachlorophenol in the environment (Wong and Crosby, 1981). The wastewaters from paper and pulp plants may also contain chloranil (Stom et al., 1975).

Increased mortality and abnormal development were observed in Xenopus laevis tadpoles exposed to 0.5-2.0 mg/ℓ (Anderson and Prahlad, 1976). Latypova (1976) reported that 0.1 mg/ℓ killed some Daphnia and 10 mg/ℓ killed all Daphnia within 50-60 minutes.

Pertinent data regarding the pharmacokinetics and metabolism of chloranil were not located in the available literature cited in the Appendix.

Chloranil appeared to be carcinogenic to B6C3F1 mice treated orally (3 weeks by gavage, followed by ~80 weeks of dietary administration) with a TWA dose of 89 mg/kg/day, as demonstrated by statistically significant increased incidences of pulmonary adenomas and hepatomas in males and hepatomas in females compared with controls (BRL, 1968; Innes et al., 1969).

According to U.S. EPA (1984) guidelines for evaluating carcinogenicity evidence, the animal studies are considered to be "limited" evidence of carcinogenicity; a Group C ranking. As such, chloranil is considered to be possibly carcinogenic for humans. Chloranil was negative for reverse mutation in Salmonella typhimurium strain TA100 without metabolic activation; it was not tested with metabolic activation (Rapson et al., 1980). The lack of further studies precludes the evaluation of chloranil as a mutagen. Pertinent data regarding the teratogenicity or other reproductive effects of chloranil could not be located in the available literature as cited in the Appendix. In the carcinogenicity study by BRL (1968), significantly increased incidences of focal pneumonia were observed in treated male and female B6C3F1 and female B6AKF1 mice compared with controls. Because the controls were housed randomly in the same rooms as the treated mice, the possibility was suggested that the chloranil-treated mice were more susceptible to infection. Observations in rats treated orally with chloranil at 0.05, 10.4 or 104 mg/kg/day, 6 days/week for 7 months and observed for an

additional 2 months (Latypova, 1976) support the suggestion that chloranil adversely affected the immune system (e.g., at 10.4 mg/kg/day, macrophage activity was decreased, and at 104 mg/kg/day, the percentage of total globulins was decreased). Effects on the hematological system were also observed at $\geq$10.4 mg/kg/day and reduced body weight gain and unspecified histological lesions were observed at 104 mg/kg/day. No effects were observed at 0.05 mg/kg/day. The acute oral LD_{50} for chloranil in rats ranges from 4000-6951 mg/kg (Windholz, 1983; Martin and Worthing, 1977; NIOSH, 1985; Hess et al., 1982).

A q_1^* for humans of 4.03×10^{-1} $(mg/kg/day)^{-1}$ was derived from the incidence of hepatomas and lung adenomas in male B6C3F1 mice treated orally with chloranil at a TWA dose of 89 mg/kg/day for ~18 months in the BRL (1968) study. The q_1^* is recommended for estimating the increased lifetime cancer risk of human exposure to chloranil.

An RQ for chronic toxicity of 1000 was derived for chloranil based on the effect of immunosuppression in rats treated orally with chloranil at 10.4 mg/kg/day, 6 days/week for 7 months and observed for an additional 2 months in the study by Latypova (1976).

The available carcinogenicity data for chloranil are limited, which places chloranil in IARC Group 3 and EPA Group C (U.S. EPA, 1984). A potency factor (F) of 2.17 $(mg/kg/day)^{-1}$ was derived from the incidence of hepatomas and lung adenomas in male B6C3F1 mice treated orally with chloranil at a TWA dose of 89 mg/kg/day for ~18 months. The magnitude of F indicates that chloranil is a Potency Group 3 chemical with a LOW hazard ranking under CERCLA, which corresponds to an RQ of 1000 pounds.

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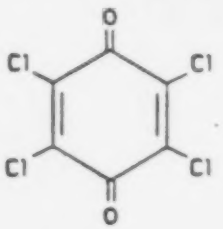
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
BOD	Biological oxygen demand
CAS	Chemical Abstract Service
CS	Composite Score
LC_{50}	Concentration lethal to 50% of recipients
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TLC	Thin-layer chromatography

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The chemical commonly known as chloranil is also known by its chemical names 2,3,5,6-tetrachloro-2,5-cyclohexadiene-1,4-dione; 2,3,5,6-tetrachloro-p-benzoquinone; tetrachloroquinone and 2,3,5,6-tetrachloro-1,4-benzoquinone (Windholz, 1983; NIOSH, 1985). Some of the common trade names for this compound are Reranil, Spergon, Vulklor and G-444E (NIOSH, 1985). The structure, empirical formula and molecular weight for chloranil are as follows:



Empirical formula: $C_6Cl_4O_2$

Molecular weight: 245.89

The CAS Registry number for chloranil is 118-75-2.

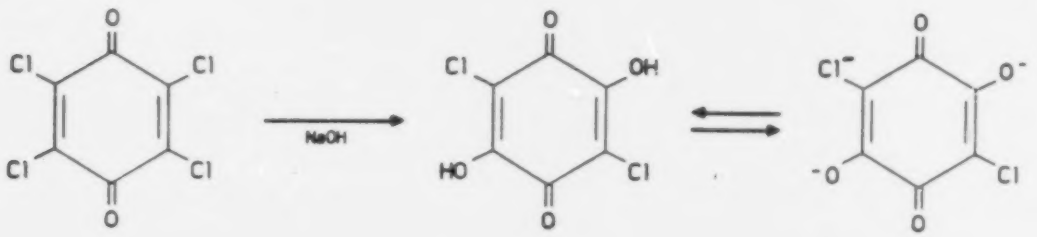
1.2. PHYSICAL AND CHEMICAL PROPERTIES

Chloranil is a yellow crystalline solid with a weak characteristic odor (Latypova, 1976). It is soluble in ethyl ether but sparingly soluble in chloroform, carbon tetrachloride and carbon disulfide (Windholz, 1983). Some of the physical properties of chloranil are listed below:

Melting point:	290°C	Hawley, 1981
Specific gravity:	1.97	Hawley, 1981
Vapor pressure:		
at 70.7°C	1.00 mm Hg	Perry and Green, 1984
at 25°C	7.6×10^{-8} mm Hg (estimated)	Perry and Green, 1984
Water solubility in distilled water at room temperature:	250 mg/ℓ	Martin and Worthing, 1977

Henry's Law constant: at 25°C	0.98×10^{-5} atmos·m³/mol (estimated)	
Log K_{ow}:	2.60 (estimated)	Hansch and Leo, 1985
Log K_{oc} :	2.32 (estimated)	Kenaga, 1980
Odor threshold in drinking water:	3.5 mg/ℓ	Latypova, 1976
Taste threshold in drinking water:	2.1 mg/ℓ	Latypova, 1976

Chloranil is chemically stable under normal conditions; however, two of the four chlorine atoms in the para-position of chloranil are easily substituted to form dye intermediates (Windholz, 1983). In alkaline solution, chloranil undergoes similar substitution reactions to form salts of chloroanilic acid (Martin and Worthing, 1977) according to the following reaction:



1.3. PRODUCTION DATA

The TSCA Inventory (U.S. EPA, 1977a) lists the following companies as the importers of chloranil in the United States before 1977:

BASF Wyandotte Corp., Parsippany, NJ
American Cyanamid Co., Bound Brook, NJ
American Hoechst Corp., Bridgewater, NJ
Uniroyal, Inc., Naugatuck, CT
Chugai Boyeki (America) Corp., New York, NY

According to the TSCA Inventory (U.S. EPA, 1977a), both Uniroyal, Inc. and Chugai Boyeki Corp. each imported 10,000-100,000 pounds of chloranil in the United States in 1976. Data regarding imported quantities for the other three companies are not available. Aceto Chemical Co., Inc., Flushing, NY, the only U.S. producer of pesticide products containing chloranil, cancelled its U.S. EPA registration in February, 1977 (U.S. EPA, 1977b). According to SRI (1985) and USITC (1984), chloranil is not currently produced in the United States. Chloranil is manufactured by treating phenol, p-chlorophenol or p-phenylenediamine with potassium chlorate and hydrochloric acid (Hawley, 1981). Chloranil has also been synthesized by the reaction of phenol or hydroquinone with concentrated hydrochloric acid/30% hydrogen peroxide and magnesium chloride as a catalyst (Luebbecke and Boldt, 1978).

1.4. USE DATA

Chloranil has been used in the United States as an agricultural fungicide. It can also be used as a dye intermediate, electrodes for pH measurements and as a chemical reagent (Hawley, 1981).

1.5. SUMMARY

Chloranil is a yellow crystalline solid with a weak characteristic odor (Latypova, 1976). It has a water solubility of 250 mg/ℓ at room temperature but is readily soluble in ether (Martin and Worthing, 1977). Chloranil is chemically stable under normal conditions; however, two of the four chlorine atoms in the para-position of chloranil are easily substituted under certain reaction conditions (Windholz, 1983).

Although the TSCA Inventory (U.S. EPA, 1977a) lists five companies as importers of chloranil in the United States before 1977, this chemical is not currently produced in the United States (SRI, 1985; USITC, 1984).

Aceto Chemical Co., Inc., Flushing, NY, the only U.S. producer of pesticide products containing chloranil, cancelled its U.S. EPA registration in February, 1977 (U.S. EPA, 1977b). Chloranil is manufactured by treating phenol, p-chlorophenol or p-phenylenediamine with potassium chlorate and hydrochloric acid (Hawley, 1981). Currently, this chemical is apparently used only for dye and electrode manufacture, and as a chemical reagent (Hawley, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

Pertinent data regarding the fate and transport processes for chloranil in the atmosphere were not located in the available literature; however, some predictions about the atmospheric fate can be made by analogy to its observed aquatic reactions (Section 2.2). The two observed photochemical processes, photoreduction of chloranil to tetrachlorohydroquinone and the displacement of a chlorine by hydroxyl to form trichlorohydroxy-p-benzoquinone, are not likely to occur in the atmosphere. Since the two para-carbonyl groups in chloranil are already in the oxidized state, it is unlikely that significant oxidation of this compound will occur with atmospheric oxidants (i.e., chloranil is expected to be stable toward the likely chemical and photochemical processes in the atmosphere). Significant removal of chloranil through sorption on atmospheric aerosol particles and subsequent precipitation, and removal by sorption upon impaction on the earth's surface (dry deposition) is not likely to occur (Cupitt, 1980). Considering the aqueous solubility of chloranil, however, slight removal of this compound through dissolution into raindrops or entrapment by snow and subsequent precipitation is likely. The overall physical removal mechanisms, however, are not likely to remove significant amounts of atmospheric chloranil.

2.2. WATER

Pertinent data regarding the hydrolysis of chloranil in natural aquatic media could not be located in the available literature. Although chloranil forms salts of chloroanilic acid with alkalis (Martin and Worthing, 1977), it is unlikely that significant hydrolysis of chloranil will occur between pH 6 and 9.

The photolysis of chloranil in ethanol and methanol was studied by Fisch and Hemmerlin (1972) and Hemmerlin (1973). When the solutions were exposed to Southern California sunlight, both tetrachlorohydroquinone and trichlorohydroquinone were produced. Although no kinetic data for this reaction were provided by the authors, the quantum yield data (quantum yield of 0.022 in 95% ethanol solution) indicate that this reaction may be significant in alcohol solutions. The reaction of chloranil in aqueous solution under irradiation with sunlight was not studied by these authors, but it is likely that photochemical reaction may be significant.

Oduntan and Odeyemi (1984) investigated the persistence of chloranil in sewage water, freshwater and seawater by studying the disappearance rate of 50 µg/ℓ spiked chloranil in samples of both sterilized and nonsterilized water in flasks not protected against sunlight. The complete disappearance of chloranil from sterilized and nonsterilized sewage water occurred in 28 and 20 days, respectively. Therefore, both biodegradation and chemical degradation was responsible for the degradation of chloranil in sewage water. The half-lives for chloranil disappearance from sterilized and nonsterilized sewage water were 7 and 4 days, respectively. Similar experiments were conducted with freshwater. The complete disappearance times for chloranil from sterilized and nonsterilized freshwater were estimated to be 28 and 24 days, respectively, while the half-lives were estimated to be 8 and 5 days, respectively. In seawater, chloranil completely disappeared in 28 weeks in both sterilized and nonsterilized samples. The half-life for chloranil in seawater under both sterile and nonsterile conditions was ~18 weeks; however, some biodegradation seemed to occur in the first 15 weeks, since the compound disappeared slightly faster during this period in the nonsterilized samples. These experimental results, however, should be

interpreted with caution because the disappearance times and the half-lives may not be due to chemical, photochemical and biological reactions alone. Volatilization from water may have contributed partly to the disappearance of chloranil since the experiments were not conducted in closed flasks; however, volatilization may not play a significant role in the disappearance of chloranil from water.

Pertinent data regarding the rate of volatilization of chloranil from water could not be located in the available literature; however, the estimated Henry's law constant of 0.98×10^{-5} atmos·m³/mol at 25°C and the volatility characteristics associated with various ranges of Henry's law constant (Lyman et al., 1982) indicate that the volatilization of chloranil from water will be slow. Similarly, the estimated K_{oc} of 210 (see Section 1.2.) indicates that a moderate amount of this compound will be removed from the aquatic phase by adsorption onto particular matters present in water.

The estimated BCF for chloranil is 27 (Kenaga, 1980), indicating that chloranil is not expected to bioconcentrate significantly in aquatic organisms.

2.3. SOIL

Only a limited number of studies are available regarding the fate of chloranil in soil. Oduntan and Odeyemi (1984) observed the disappearance rate of chloranil in spiked (50 µg/g of soil) natural soil under both sterile and nonsterile conditions. The soil was incubated in flasks not protected against sunlight. Besides biodegradation, chemical and photochemical reactions were responsible for the disappearance of chloranil. Part of the observed disappearance could also be attributed to volatilization from soil since the experiments were not conducted in closed flasks.

In sterile and nonsterile soil, chloranil disappeared completely in 41 and 28 days, respectively. The half-lives of chloranil disappearance from sterile and nonsterile soils were estimated to be 18 and 6 days, respectively. It can be concluded from the results of these experiments that biodegradation may be important in the removal of chloranil from soil. Although chemical degradation was partly responsible for the disappearance of chloranil from soil, it is impossible to predict whether photochemical reactions, hydrolysis, other chemical reactions or a combination of these reactions were responsible for the observed loss of chloranil.

Data regarding the significance of the loss of chloranil from soil through volatilization were not located in the available literature. Based on its expected aqueous volatilization probability (see Section 2.2.), however, volatilization of chloranil from soil may not be significant. From the estimated K_{oc} of 210 (Kenaga, 1980) and the water solubility of 250 mg/ℓ (see Section 1.2.), chloranil can be predicted to be moderately mobile in soil. The results of soil TLC experiments with Hagerstown silty clay loam soil (K_{oc}=2.50%) showed that chloranil was immobile (Helling et al., 1974). Considering its low mobility and relatively high rate of biodegradation in soil, chloranil is not expected to leach into groundwater from most soils; however, leaching may be possible from soils with low organic carbon contents but relatively high levels of chloranil. The toxicity of high concentrations of chloranil towards microbial populations in soil may retard or inhibit the biodegradation process, leading to accelerated leaching.

2.4. SUMMARY

The fate and transport of chloranil in the environment has not been studied comprehensively. Based on its physical properties and the limited

reactivity data available in aquatic media, chloranil is not expected to undergo significant chemical or photochemical reactions in the atmosphere. It has also been speculated that small amounts of chloranil will be removed from the atmosphere through wet deposition and that other physical removal mechanisms are not likely to be significant. Therefore, chloranil is expected to be persistent in the atmosphere.

From the limited data provided by Fisch and Hemmerlin (1972), it has been concluded that chloranil will undergo significant photochemical reaction in water. Biodegradation of chloranil in water may also be important (Oduntan and Odeyemi, 1984). The half-lives for chloranil disappearance from sterile and nonsterile sewage water have been estimated to be 7 and 4 days, respectively. The corresponding values in freshwater are 8 and 5 days; however, the half-life of chloranil in seawater has been estimated to be 18 weeks. Therefore, chloranil may not persist in most natural freshwaters, but it may be persistent in seawater (Oduntan and Odeyemi, 1984). Based on its physical properties, a significant loss of chloranil through volatilization from water is not expected to occur, but moderate removal of chloranil through precipitation of sorbed chloranil into aquatic particulate matter is expected to occur. Chloranil will not bioconcentrate significantly in aquatic organisms.

In the soil, significant removal of chloranil will take place through biodegradation. The overall half-life of chloranil in soil has been estimated to be 6 days (Oduntan and Odeyemi, 1984). The experimental results of Helling et al. (1974) show that chloranil will have low mobility in soil. Based on this mobility and significantly high biodegradation rate in soil, it has been predicted that chloranil will not leach into groundwater under most conditions.

3. EXPOSURE

Pertinent data regarding the level of chloranil in the environment could not be located in the available literature as cited in the Appendix. Since chloranil is no longer manufactured in the United states, the principal sources of chloranil in the environment are expected to be user sites, such as dye and electrode manufacturers. Small amounts of chloranil may also originate from the photodecomposition of pentachlorophenol in the environment (Wong and Crosby, 1981). The wastewaters from paper and pulp plants may also contain chloranil (Stom et al., 1975).

4. PHARMACOKINETICS

Pertinent data regarding the absorption, distribution, metabolism or excretion of chloranil by laboratory animals or humans could not be located in the available literature as cited in the Appendix.

5. EFFECTS

5.1. CARCINOGENICITY

In an early carcinogenicity bioassay, groups of 18 male and 18 female B6C3F1 and 18 male and 18 female B6AKF1 mice were treated with chloranil for ~18 months (BRL, 1968; Innes et al., 1969). The mice were treated by gavage with chloranil in 5% gelatin at a dose of 215 mg/kg/day (determined from the average body weight at 7 days of age and not corrected for subsequent body weight gain) from days 7-28 of age, and then in the diet at 646 ppm for 79-81 weeks (TWA=89 mg/kg/day, Table 5-1). Negative controls consisted of untreated and vehicle-treated male and female mice of both strains (90 mice/sex/strain). The incidences of tumors are presented in Table 5-1. Statistical analysis of the data was performed at SRC using the Fisher Exact test. Significantly increased incidences of pulmonary adenomas and hepatomas (all liver tumors) were found in treated male B6C3F1 mice compared with controls. In female B6C3F1 mice, the incidence of hepatomas was also significantly greater compared with controls.

Innes et al. (1969) concluded that the carcinogenic potential of chloranil requires additional evaluation; however, more recent carcinogenicity studies were not located in the available literature, and this chemical is not scheduled for testing by the National Toxicology Program (NTP, 1985).

BRL (1968) also treated similar groups of mice (28 days old) with a single subcutaneous dose (464 mg/kg) of chloranil in gelatin. The mice were observed until they were ~18 months of age, at which time they were killed and necropsied. No differences in tumor incidences were observed in treated mice compared with negative controls.

TABLE 5-1

Incidence of Tumors in Two Strains of Mice Treated with Commercial Grade Chloranil by Gavage (Gelatin Vehicle) for 3 Weeks Followed by Dietary Administration for ~80 Weeks[a]

Strain	Sex	Dose[b] (mg/kg/day)	Duration of Treatment[c] (weeks)	Target Organ	Tumor Type	Tumor Incidence[d] (p value)[e]
B6C3F1	male	0	82	lymphoreticular tissue	reticulum cell sarcoma	5/79
				lung	adenoma	5/79
				liver	hepatoma	8/79
B6C3F1	male	89	82	lymphoreticular tissue	reticulum cell sarcoma	1/17
				lung	adenoma	4/17 (p=0.049)
				liver	hepatoma	7/17 (p=0.004)
B6C3F1	female	0	82	lymphoreticular tissue	reticulum cell sarcoma	4/87
				lung	adenoma	3/87
				liver	hepatoma	0/87

TABLE 5-1 (cont.)

Strain	Sex	Dose[b] (mg/kg/day)	Duration of Treatment[c] (weeks)	Target Organ	Tumor Type	Tumor Incidence[d] (p value)[e]
B6C3F1	female	89	82	lymphoreticular tissue	reticulum cell sarcoma	0/17
				lung	adenoma	0/17
				liver	hepatoma	2/17 (p=0.025)
B6AKF1	male	0	84	lymphoreticular tissue	reticulum cell sarcoma	1/90
				lung	adenoma	9/90
				liver	hepatoma	5/90
B6AKF1	male	89	84	lymphoreticular tissue	reticulum cell sarcoma	2/18
				lung	adenoma	2/18
				liver	hepatoma	1/18
B6AKF1	female	0	83	lymphoreticular tissue	reticulum cell sarcoma	3/82
				lung	adenoma	3/82
				liver	hepatoma	1/82

TABLE 5-1 (cont.)

Strain	Sex	Dose[b] (mg/kg/day)	Duration of Treatment[c] (weeks)	Target Organ	Tumor Type	Tumor Incidence[d] (p value)[e]
B6AKF1	female	89	83	lymphoreticular tissue	reticulum cell sarcoma	1/18
				lung	adenoma	1/18
				liver	hepatoma	0/18

Quality of Evidence

Strengths of Study: The compound was administered by a relevant route for a significant portion of the lifespan to both sexes of two strains of mice. Comprehensive histological examinations were performed.

Weaknesses of Study: Small number of mice per group (18). Only one dosage level was administered.

Overall Adequacy: Adequate

[a]Source: BRL, 1968

[b]TWA dose. The mice were treated by gavage at 215 mg/kg/day from day 7-28 of age, followed by dietary administration at 646 ppm for 79-81 weeks. The dietary level is equivalent to 84 mg/kg/day assuming that a mouse consumes a daily amount of food equal to 13% of its body weight. The dose is calculated as the TWA of 215 mg/kg/day for 3 weeks and 84 mg/kg/day for 79-81 weeks.

[c]The duration of treatment is equal to the duration of the study

[d]Number of mice with tumors/number of mice necropsied

[e]Fisher Exact tests comparing the tumor incidence in treated mice with that of control were performed at SRC. Where no value appears, $p>0.05$.

In conclusion, chloranil appeared to be carcinogenic to B6C3F1 mice treated orally with a TWA dose of 89 mg/kg/day, as demonstrated by statistically significant increased incidences of pulmonary adenomas and hepatomas in males and hepatomas in females compared with controls (BRL, 1968; Innes et al., 1969).

5.2. MUTAGENICITY

Rapson et al. (1980) reported negative results for chloranil at 10^{-1} to 10^{3} µg/plate in a reverse mutation assay using Salmonella typhimurium TA100. No metabolic activation system was used. Based on these limited data, it is not possible to draw conclusions regarding the mutagenicity of chloranil.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of chloranil were not located in the available literature cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of chloranil were not located in the available literature cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The BRL (1968) carcinogenicity study of chloranil (see Section 5.1.) also provided information regarding possible treatment-related non-neoplastic lesions. In this study, male and female B6C3F1 and B6AKF1 strain mice were treated orally with chloranil at a TWA dose of 89 mg/kg/day for ~18 months. High incidences of focal pneumonia were observed in the treated mice (Table 5-2). Although pneumonia is a common lesion found in mice housed in colonies, statistical analysis performed at SRC revealed that the increased incidences in treated male and female B6C3F1 mice and female B6AKF1 mice were highly significant compared with controls. Since the

TABLE 5-2

Incidence of Focal Pneumonia in Mice Treated Orally with Chloranil for ~18 Months Compared With Controls[a,b]

Strain	Sex	Incidence of Pneumonia (%)[c]		p value[d]
		Control	Treated	
B6C3F1	male	7/79 (9)	11/17 (65)	0.000003
	female	5/87 (6)	9/17 (53)	0.00001
B6AKF1	male	26/90 (29)	4/18 (22)	0.398
	female	7/82 (9)	7/18 (39)	0.003

[a]Source: BRL, 1968

[b]The mice were treated orally at a TWA dose of 89 mg/kg/day (see Section 5.1. for details of dosing regimen)

[c]Incidence expressed as number of mice with focal pneumonia/number of mice necropsied

[d]Fisher Exact test performed at SRC

control mice were housed randomly in the same rooms as the treated mice, the higher incidence in treated mice cannot be explained fully by the housing conditions. Although the relatively high incidence of focal pneumonia in B6AKF1 control males cannot be explained, the highly significant differences between the treated mice and the other three control groups suggest a possible increased susceptibility of the treated mice to infection.

Latypova (1976) treated 70 white male and female rats (not otherwise specified) by gavage with chloranil in a 1% starch solution at 0.05, 10.4 or 104 mg/kg/day, 6 days/week for 7 months, followed by a 2-month observation period. The use of control rats was not mentioned. No effects were observed at 0.05 mg/kg/day. Rats treated with 10.4 mg/kg/day had reduced erythrocyte counts, hemoglobin concentrations, white blood cell counts, percentage lymphocytes and macrophage activity (decrease in the percentage digestion of microbes). At 104 mg/kg/day, rats had reductions in body weight gain (females), hemoglobin concentration, numbers of reticulocytes, white blood cells and percentage of total globulins and increases in albumin-to-globulin ratios, serum cholinesterase, ceruloplasmin and fructose phosphate aldolase. It was not stated whether these indices were reduced relative to concurrent controls, to historical values for rats or to pretreatment values of the experimental rats. Unspecified histological changes in unspecified organs were observed in rats treated with 104 mg/kg/day. It was unclear from the translation of this study if histological lesions were also observed at 10.4 mg/kg/day.

The observation by Latypova (1976) that chloranil treated rats had immunosuppressive effects (decreased total globulins, decreased macrophage activity) supports the suggestion that chloranil treatment increased the susceptibility of mice to infection (BRL, 1968).

Martin and Worthing (1977) reported that rats fed a diet containing 5000 ppm chloranil for an unspecified period of time had no adverse effects. Additional details were not provided.

Thus, chronic treatment with chloranil may have adversely affected the immune system of mice at 89 mg/kg/day (BRL, 1968) and resulted in hematological and immunosuppressive effects in rats at $\geq$10.4 mg/kg/day and reduced body weight gain and unspecified histological lesions in rats at 104 mg/kg/day (Latypova, 1976).

5.6. OTHER RELEVANT INFORMATION

The reported values for the acute oral LD_{50} of chloranil in rats are 4000 mg/kg (Windholz, 1983; Martin and Worthing, 1977; NIOSH, 1985) and 6951 mg/kg (Hess et al., 1982).

Yoshida et al. (1979) and Murakami and Fukami (1983) reported IC_{50} values for toxicity of chloranil to cultured cell lines measured by the cell number method and by inhibition of respiration. The IC_{50} values for reduced cell numbers were 7.08×10^{-5} M for cultured ovarian cells of the mosquito Culex pipiens and 1.38×10^{-5} M for cultured subcutaneous L cells of mice. The IC_{50} values for inhibition of respiration were 5.13×10^{-5} M for Culex cells and 2.95×10^{-5} M for L cells.

5.7. SUMMARY

Chloranil appeared to be carcinogenic to B6C3F1 mice treated orally (3 weeks by gavage, followed by ~80 weeks of dietary administration) with a TWA dose of 89 mg/kg/day, as demonstrated by statistically significant increased incidences of pulmonary adenomas and hepatomas in males and hepatomas in females compared with controls (BRL, 1968;). Chloranil was negative for reverse mutation in Salmonella typhimurium strain TA100 without metabolic activation; it was not tested with metabolic activation (Rapson et al.,

1980). The lack of further studies precludes the evaluation of chloranil as a mutagen. Pertinent data regarding the teratogenicity or other reproductive effects of chloranil were not located in the available literature. In the carcinogenicity study by BRL (1968), significantly increased incidences of focal pneumonia were observed in treated male and female B6C3F1 and female B6AKF1 mice compared with controls. Because the controls were housed randomly in the same rooms as the treated mice, the possibility was suggested that the chloranil-treated mice were more susceptible to infection. Observations in rats treated orally with chloranil at 0.05, 10.4 or 104 mg/kg/day, 6 days/week for 7 months and observed for an additional 2 months (Latypova, 1976) support the suggestion that chloranil adversely affects the immune system. For example, at 10.4 mg/kg/day, macrophage activity was decreased, and at 104 mg/kg/day, the percentage of total globulins was decreased. Effects on the hematological system were also observed at $\geq$10.4 mg/kg/day, and reduced body weight gain and unspecified histological lesions were observed at 104 mg/kg/day. No effects were observed at 0.05 mg/kg/day. The acute oral LD_{50} for chloranil in rats ranges from 4000-6951 mg/kg (Windholz, 1983; Martin and Worthing, 1977; NIOSH, 1985; Hess et al., 1982).

6. AQUATIC TOXICITY

6.1. ACUTE

Exposure to 2.0 mg/ℓ chloranil caused 100% mortality of Xenopus laevis tadpoles after 3 days (Anderson and Prahlad, 1976). Latypova (1976) reported that "some Daphnia" died at 0.1 mg/ℓ, and that all Daphnia died within 50-60 minutes at 10 mg/ℓ. The species used was not reported.

6.2. CHRONIC

Groups of 30 Xenopus laevis tadpoles were exposed to 0 (control), 0.5, 1.0, 1.25, 1.5, 1.75 and 2.0 mg/ℓ chloranil for 1-10 days. Mortality was 100% at 2.0 mg/ℓ; no mortality occurred in controls. Mortality was dose-dependent between these two extremes, but was only slightly increased at 0.5 mg/ℓ. Concentrations of 0.75-1.75 mg/ℓ affected development, causing abnormal otoliths and optic cups and incomplete pigmentation of the retina (Anderson and Prahlad, 1976).

6.3. PLANTS

Pertinent data regarding the toxicity of chloranil to aquatic plants were not located in the available literature cited in the Appendix.

6.4. RESIDUES

Pertinent data regarding chloranil residues in aquatic organisms were not located in the available literature cited in the Appendix.

6.5. OTHER RELEVANT INFORMATION

Chloranil concentrations of 1.0 and 10.0 mg/ℓ inhibited BOD in reservoirs, while 0.01 and 0.1 mg/ℓ did not (Latypova, 1976).

6.6. SUMMARY

Increased mortality and abnormal development were observed in Xenopus laevis tadpoles exposed to 0.5-2.0 mg/ℓ (Anderson and Prahlad, 1976). Latypova (1976) reported that 0.1 mg/ℓ killed some Daphnia and 10 mg/ℓ killed all Daphnia within 50-60 minutes.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The U.S. EPA cancelled registration for pesticide products containing chloranil at the request of the Aceto Chemical Co., Inc., which was stated to be the only Federal registrant of pesticide products containing chloranil (U.S. EPA, 1977b). No reason for the cancellation was given.

7.2. AQUATIC

Latypova (1976) recommended a maximum admissible concentration of 0.1 mg/ℓ for reservoir water. This value is based on organoleptic effects, but is also the threshold for toxicity to Daphnia and microorganisms. No U.S. guidelines or standards for the protection of aquatic organisms from the toxic effects of chloranil were located in the available literature.

8. RISK ASSESSMENT

Chloranil appeared to be carcinogenic to B6C3F1 mice treated orally (3 weeks by gavage, followed by ~80 weeks of dietary administration) with a TWA dose of 89 mg/kg/day, as demonstrated by statistically significant increased incidences of pulmonary adenomas and hepatomas in males and hepatomas in females compared with controls (BRL, 1968). Chloranil was negative for reverse mutation in Salmonella typhimurium strain TA100 without metabolic activation; it was not tested with metabolic activation (Rapson et al., 1980). The lack of further studies precludes the evaluation of chloranil as a mutagen. Pertinent data regarding the teratogenicity or other reproductive effects of chloranil were not located in the available literature. In the carcinogenicity study by BRL (1968), significantly increased incidences of focal pneumonia were observed in treated male and female B6C3F1 and female B6AKF1 mice compared with controls. Because the controls were housed randomly in the same rooms as the treated mice, the possibility was suggested that the chloranil-treated mice were more susceptible to infection. Observations in rats treated orally with chloranil at 0.05, 10.4 or 104 mg/kg/day, 6 days/week for 7 months and observed for an additional 2 months (Latypova, 1976) support the suggestion that chloranil adversely affects the immune system. For example, at 10.4 mg/kg/day, macrophage activity was decreased, and at 104 mg/kg/day, the percentage of total globulins was decreased. Effects on the hematological system were also observed at $\geq$10.4 mg/kg/day, and reduced body weight gain and unspecified histological lesions were observed at 104 mg/kg/day. No effects were observed at 0.05 mg/kg/day. Martin and Worthing (1977) reported that rats treated with chloranil at a dietary concentration of 5000 ppm for an unspecified period of time had no adverse effects; additional details were not provided.

Since chloranil appeared to be carcinogenic to mice (BRL, 1968), it is appropriate to derive a q_1^*. The tumor incidences and data used to calculate the q_1^* values are presented in Tables 8-1 to 8-4. The transformed dose was calculated by converting the dietary concentration of 646 ppm to 84.0 mg/kg/day, assuming that a mouse consumes a daily amount of food equal to 13% of its body weight (U.S. EPA, 1980), and taking the TWA of 215 mg/kg/day for 3 weeks and 84.0 mg/kg/day for 79 weeks. The unadjusted q_1^* values were calculated using the computerized multistage model (GLOBAL 82) developed by Howe and Crump (1982). The unadjusted q_1^* values were corrected for interspecies dose extrapolation by multiplying by the cube root of the ratio of the reference human body weight (70 kg) to the average weight of the male mice (0.045 kg) or of the female mice (0.038 kg) in the BRL (1968) study. Since the length of the experiment was less than the 104-week lifespan of the mouse, a further correction for late developing tumors was made by multiplying by the cube of the ratio of the mouse lifespan to the length of the experiment (U.S. EPA, 1980).

As seen from Tables 8-1 to 8-3, a q_1^* was derived for all the statistically significant tumor incidences; that is, liver hepatomas in male mice, lung adenomas in male mice and liver hepatomas in female mice. The highest q_1^* resulted from the data on liver hepatomas in male mice, and this value, 2.22×10^{-1} $(mg/kg/day)^{-1}$, could be used to estimate the increased lifetime risk of human exposure to chloranil. According to the U.S. EPA (1984), however, "to obtain a total estimate of carcinogenic risk, animals with one or more tumor sites or types showing significantly elevated tumor incidence should be pooled and used for extrapolation." BRL (1968) did not provide individual animal pathology data. As a first approximation, however, the incidences of lung and liver tumors in the male B6C3F1 mice can be

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: chloranil

Reference: BRL, 1968

Species, Strain, Sex: mouse, B6C3F1, male

Body weight: 0.045 kg measured

Length of exposure (le) = 82 weeks

Length of experiment (Le) = 82 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: liver, hepatoma

Route, vehicle: gavage, gelatin for 3 weeks, then diet for 79 weeks

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
215 mg/kg/day for 3 weeks, then 646 ppm in diet for 79 weeks	89	7/17
0	0	8/79

Unadjusted q_1^* from study = 9.410082×10^{-3} $(mg/kg/day)^{-1}$
Human q_1^* = 2.2244042×10^{-1} $(mg/kg/day)^{-1}$

TABLE B-2

Cancer Data Sheet for Derivation of q_1^*

Compound: chloranil

Reference: BRL, 1968

Species, Strain, Sex: mouse, B6C3F1, male

Body weight: 0.045 kg measured

Length of exposure (le) = 82 weeks

Length of experiment (Le) = 82 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: lung, adenoma

Route, vehicle: gavage, gelatin for 3 weeks, then diet for 79 weeks

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
215 mg/kg/day for 3 weeks, then 646 ppm in diet for 79 weeks	89	4/17
0	0	5/79

Unadjusted q_1^* from study = 5.53394×10^{-3} $(mg/kg/day)^{-1}$
Human q_1^* = 1.30814×10^{-1} $(mg/kg/day)^{-1}$

TABLE 8-3

Cancer Data Sheet for Derivation of q_1^*

Compound: chloranil

Reference: BRL, 1968

Species, Strain, Sex: mouse, B6C3F1, female

Body weight: 0.038 kg measured

Length of exposure (le) = 82 weeks

Length of experiment (Le) = 82 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: liver, hepatoma

Route, vehicle: gavage, gelatin for 3 weeks, then diet for 79 weeks

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
215 mg/kg/day for 3 weeks, then 646 ppm in diet for 79 weeks	89	2/17
0	0	0/87

Unadjusted q_1^* from study = 3.7329033×10^{-3} $(mg/kg/day)^{-1}$
Human q_1^* = 9.3356239×10^{-2} $(mg/kg/day)^{-1}$

TABLE 8-4

Cancer Data Sheet for Derivation of q_1^*

Compound: chloranil

Reference: BRL, 1968

Species, Strain, Sex: mouse, B6C3F1, male

Body weight: 0.045 kg measured

Length of exposure (le) = 82 weeks

Length of experiment (Le) = 82 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: liver, hepatoma or lung, adenoma

Route, vehicle: gavage, gelatin for 3 weeks, then diet for 79 weeks

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
215 mg/kg/day for 3 weeks, then 646 ppm in diet for 79 weeks	89	11/17
0	0	13/79

Unadjusted q_1^* from study = 1.7036094×10^{-2} $(mg/kg/day)^{-1}$
Human q_1^* = 4.0270808×10^{-1} $(mg/kg/day)^{-1}$

added to provide a pooled incidence (see Table 8-4). This pooled incidence may overestimate the number of mice with tumors. The resultant q_1^* of 4.03×10^{-1} $(mg/kg/day)^{-1}$ is slightly higher than the sum of the individual q_1^* values obtained from the liver tumor data (see Table 8-1) and the lung tumor data (see Table 8-2). Since according to U.S. EPA (1984), "the pooled estimate will generally be used in preference to risk estimates based on single sites or types," the q_1^* of 4.03×10^{-1} $(mg/kg/day)^{-1}$ is recommended for estimating the increased lifetime risk of human exposure to chloranil.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The effects of chronic oral exposure to chloranil were discussed in Section 5.5. and are summarized in Table 9-1. It should be noted that in the BRL (1968) study, B6C3F1 mice had significantly increased incidences of hepatomas and pulmonary adenomas (see Section 5.1.) in addition to the increased incidences of focal pneumonia. Although respiratory disorders are commonly observed in mouse colonies, the fact that the control mice were housed in the same rooms as the treated mice suggested that the increased incidence of focal pneumonia was a result of chloranil-induced suppression of the immune system. The findings of decreased macrophage activity and decreased total serum globulins in rats treated with chloranil in the Latypova (1976) study support the immunosuppressive activity of chloranil.

Data used to calculate the MEDs and CSs are presented in Table 9-2. The lowest dose at which evidence of immunosuppression (decreased macrophage activity) was observed is 8.9 mg/kg/day in the study by Latypova (1976). The human MED of 107 mg/day was calculated by multiplying the animal transformed dose by the cube root of the ratio of the rat body weight, assumed to be 0.35 kg (U.S. EPA, 1980), to the reference human body weight (70 kg), and by 70 kg. The MED corresponds to an RV_d of 2.5. An RV_e of 7 can be assigned to this effect because there was a change in physiological activity. Multiplying the RV_d by the RV_e results in a CS of 17.5, which corresponds to an RQ of 1000.

A CS can also be derived for the increased incidence of focal pneumonia, since, although it may have resulted from suppression of the immune system, it represents pulmonary dysfunction, which warrants an RV_e of 8. The MED of 508 mg/day was calculated from the mouse dose of 89 mg/kg/day in the BRL

TABLE 9-1

Oral Toxicity Summary for Chloranil

Species/ Strain	Sex	Vehicle/ No. at Start	Physical State	Purity	Dosage/Exposure	Transformed Dose (mg/kg/day)	Response	Reference
Mouse/ B6C3F? and B6AKF1	M,F	18/sex/ strain	gelatin then diet	commercial grade	215 mg/kg/day for 3 weeks (gavage) followed by 646 ppm in diet for ~80 weeks	89[a]	Significantly (p=0.003-0.000003) increased incidence of focal pneumonia, possibly resulting from increased susceptibility to infection.	BRL, 1968
Rat/NR	M,F	<70	starch	NR	10.4 mg/kg/day 6 days/week for 7 months, followed by 2 months observation	8.9[b]	Reductions in erythrocyte count, hemoglobin concentration, white blood cell count, percentage of lymphocytes and macrophage activity. Possible histological lesions in unspecified organs.	Latypova, 1976
Rat/NR	M,F	<70	starch	NR	104 mg/kg/day, 6 days/week for 7 months, followed by 2 months observation	89[b]	Reductions in body weight gain, hemoglobin concentration, reticulocyte number, white blood cell count, percentage total globulins; increases in albumin-to-globulin ratio, serum cholinesterase ceruloplasmin and fructose phosphate aldolase. Unspecified histological lesions in unspecified organs.	Latypova, 1976

[a]The transformed dose was calculated by converting the dietary concentration of 646 ppm to 84.0 mg/kg/day, assuming that a mouse consumes a daily amount of food equal to 13% of its body weight and by taking the TWA of 215 mg/kg/day for 3 weeks and 84.0 mg/kg/day for 79-81 weeks.

[b]The transformed dose was calculated by expanding the dose over a 7-day week (10.4 mg/kg/day x 6 days/7 days = 6.9 mg/kg/day).

TABLE 9-2

Oral Composite Scores for Chloranil

Species	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
Mouse	89	508	1.4	Focal pneumonia, possibly as a result of suppression of immunological system	8	11.2	1000	BRL, 1968
Rat	8.9	107	2.5	Suppression of immunological system (decreased macrophage activity)	7	17.5	1000	Latypova, 1976

(1968) study by multiplying by the cube root of the mouse body weight (0.038 kg for females in the study) to the human body weight and by 70 kg. The MED corresponds to an RV_d of 1.4. The CS is 11.2, which also corresponds to an RQ of 1000.

Other effects in rats observed by Latypova (1976) included reductions in body weight and hematological parameters and increases in some serum enzymes (see Table 9-1). These effects occurred at the higher dose, which would correspond to a lower RV_d, and the effects would warrant lower RV_es; therefore it is not necessary to calculate CSs for these effects. Latypova (1976) also reported unspecified histological lesions in treated rats, but it was unclear from the translation of this Russian study if the lesions were observed at both doses or only the high dose. Therefore, data are insufficient to calculate a CS for histological lesions.

Both CSs presented in Table 9-2 correspond to RQ values of 1000; however, the CS of 17.5 is the higher, and the study of Latypova (1976) is recommended as the basis of the RQ for chloranil (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Chloranil appeared to be carcinogenic to B6C3F1 mice treated orally with a TWA dose of 89 mg/kg/day for ~18 months, as evidenced by statistically significant increased incidences of hepatomas (all liver tumors) and pulmonary adenomas in males and hepatomas in females compared with controls (BRL, 1968). This study is summarized in Table 5-1. From this study it can be concluded that the carcinogenic potential of chloranil requires further evaluation; however, more recent studies were not located, and this chemical is not scheduled for testing by the National Toxicology Program (NTP, 1985). Using the U.S. EPA (1984) weight of evidence criteria for evaluating carcinogenicity data, the response in mice corresponds to "limited" animal

TABLE 9-3

Chloranil

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	107
Effect:	suppression of immune system
Reference:	Latypova, 1976
RV_d:	2.5
RV_e:	7
Composite Score:	17.5
RQ:	1000

*Equivalent human dose

evidence, Group C. This implies that the evidence is considered to be "possibly" carcinogenic for humans.

BRL (1968) also treated similar groups of mice with a single subcutaneous dose (464 mg/kg) of chloranil in gelatin on day 28 of age. The mice were observed until they were ~18 months of age, at which time they were killed and necropsied. No differences in tumor incidences were observed between treated and control mice.

Data regarding the carcinogenicity of chloranil in humans could not be located in the available literature. Therefore, limited evidence was available to show that chloranil is carcinogenic to animals and inadequate evidence that it is carcinogenic to humans. Based on the IARC classification scheme, chloranil is a Group 3 chemical; that is, it cannot be classified as to its carcinogenicity for humans.

Since chloranil appeared to be carcinogenic to mice (BRL, 1968), it is possible to calculate a potency factor (F or $1/ED_{10}$). As discussed in Chapter 8, a q_1^* value of 4.03×10^{-1} $(mg/kg/day)^{-1}$ was derived based on the pooled incidence of liver hepatomas and lung adenomas; therefore, it is appropriate to derive F from the same set of data (see Table 5-1). The unadjusted $1/ED_{10}$ was calculated using the computerized multistage model (GLOBAL 82) developed by Howe and Crump (1982). The unadjusted $1/ED_{10}$ of 9.19×10^{-2} $(mg/kg/day)^{-1}$ (Table 9-4) was corrected for interspecies dose extrapolation by multiplying by the cube root of the ratio of the human body weight (70 kg) to the average weight of the male mice (0.045 kg) in the BRL (1968) study. Since the length of the experiment (82 weeks) was less than the lifespan of the mouse (104 weeks), a further correction for late developing tumors was made by multiplying by $(104/82)^3$. The resulting adjusted $1/ED_{10}$ or F factor is 2.17 $(mg/kg/day)^{-1}$ (see Table 9-4).

TABLE 9-4

Derivation of Potency Factor (F) for Chloranil

Reference:	BRL, 1968	
Exposure route:	oral (gavage 3 weeks; diet 79 weeks)	
Species:	mouse	
Strain:	B6C3F1	
Sex:	male	
Vehicle or physical state:	gelatin	
Body weight:	0.045 kg	
Duration of treatment:	82 weeks	
Duration of study:	82 weeks	
Lifespan of animal:	104 weeks	
Target organs:	lungs and liver	
Tumor types:	hepatoma and adenoma	
Experimental doses/ exposure:	0	215 mg/kg/day for 3 weeks; then 646 ppm in diet for 79 weeks
Transformed doses (mg/kg/day):	0	89
Tumor incidence:	13/79	11/17
Unadjusted ED_{10}:	9.1889806×10^{-2} $(mg/kg/day)^{-1}$	
$1/ED_{10}$ (F factor):	2.1721391 $(mg/kg/day)^{-1}$	

Since the F factor falls between 1 and 10, chloranil is placed in Potency Group 3. A Potency Group 3 chemical with an IARC classification of 3 and EPA classification of C (U.S. EPA, 1984) ranks low in the Hazard Ranking scheme under CERCLA, which corresponds to an RQ of 1000 pounds.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in August, 1985 with the exception of the TOXLINE, which was searched in February, 1984 and was kindly supplied by Dynamac Corp. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

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